

1 Association of egg consumption and calcified atherosclerotic plaque in the coronary  
2 arteries: the NHLBI Family Heart Study

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- 24 Abbreviations: CHD, coronary heart disease; CAC, coronary-artery calcium; CI,
- 25 confidence interval; CVD, cardiovascular disease; CT, computed tomography; NHLBI
- 26 FHS, National Heart, Lung, and Blood Institute Family Heart Study; HDL, high-density
- 27 lipoprotein; LDL, low-density lipoprotein

28 **ABSTRACT**

## 29 Background and Aims:

30 Eggs are a ubiquitous and important source of dietary cholesterol and nutrients, yet their  
31 relationship to coronary heart disease (CHD) remains unclear. While some data have  
32 suggested a positive association between egg consumption and CHD, especially among  
33 diabetic subjects, limited data exist on the influence of egg consumption on subclinical  
34 disease. Thus, we sought to examine whether egg consumption is associated with  
35 calcified atherosclerotic plaques in the coronary arteries.

## 36 Methods:

37 In a cross-sectional design, we studied 1848 participants of the NHLBI Family Heart  
38 Study without known CHD. Egg consumption was assessed by a semi-quantitative food  
39 frequency questionnaire and coronary-artery calcium (CAC) was measured by cardiac CT.  
40 We defined prevalent CAC using an Agatston score of at least 100 and fitted generalized  
41 estimating equations to calculate prevalence odds ratios of CAC.

## 42 Results:

43 Mean age was 56.5 years and 41% were male. Median consumption of eggs was 1/week.  
44 There was no association between frequency of egg consumption and prevalent CAC.  
45 Odds ratios (95% CI) for CAC were 1.0 (reference), 0.95 (0.66-1.38), 0.94 (0.63-1.40),  
46 and 0.90 (0.57-1.42) for egg consumption of almost never, 1-3 times per month, once per  
47 week, and 2+ times per week, respectively (p for trend 0.66), adjusting for age, sex, BMI,  
48 smoking, alcohol, physical activity, income, field center, total calories, and bacon.



Additional control for hypertension and diabetes mellitus, or restricting the analysis to subjects with diabetes mellitus or fasting glucose >126 mg/dL did not alter the findings.

Conclusions:

These data do not provide evidence for an association between egg consumption and prevalent CAC in adult men and women.

KEYWORDS: egg; diet; epidemiology; subclinical disease; coronary calcium; atherosclerosis

## Introduction

Coronary heart disease (CHD) remains the leading cause of death in the United States. Elevated serum non-HDL cholesterol is strongly associated with the risk of CHD<sup>1-2</sup>, and thus the role of dietary influences on serum cholesterol has fostered much research attention. The role of egg consumption on CHD is of particular interest because of its unique nutritional qualities. Eggs are an important source of protein, minerals, and fat-soluble vitamins, but also a source of dietary cholesterol with about 200 mg of cholesterol in an average egg.<sup>3</sup>

The relationship between egg consumption and CHD remains unclear.<sup>4-5</sup> A meta-analysis of several large, prospective cohorts did not find an association between egg consumption and CHD, however subgroup analysis showed a positive relationship between egg consumption and CHD in diabetic populations.<sup>4</sup> In contrast, a recent meta-analysis involving twelve studies reported a 19% higher risk of cardiovascular disease (CVD) with higher egg consumption (83% higher risk of CVD with egg intake in diabetic

individuals).<sup>5</sup>

Coronary artery calcification (CAC) is a well-described marker for subclinical atherosclerotic disease.<sup>6-7</sup> The extent of CAC can help in risk stratification and can help predict future CHD events.<sup>8</sup> Despite limited studies of egg intake with CVD, no study has investigated whether egg consumption is associated with subclinical CHD.

Hence, the present study sought to determine whether egg consumption was associated with a lower prevalence of CAC in individuals without known coronary heart disease.

## Materials and methods

### *1. Study population*

Participants in this study were members of the National Heart, Lung, and Blood Institute Family Heart Study (NHLBI FHS) in whom coronary calcified plaque was measured by cardiac-gated multi-detector computed tomography (cardiac CT). The NHLBI FHS is a multi-center, population-based study designed to identify and evaluate genetic and non-genetic determinants of CHD, preclinical atherosclerosis, and cardiovascular risk factors, and has been described in detail in previous publications.<sup>9-10</sup> Briefly, families in the study had been chosen randomly (random group) or based on a higher than expected risk of CHD (high-risk group) from previously established population-based cohort studies. A total of 588 families were chosen at random (with 2673 subjects) and 566 families were selected based on higher than expected risk of CHD (3037 subjects). Of the 5710 subjects, 265 were African-American. The high-risk group

was defined based on a family risk score, which compares the family's age and sex-specific incidence of CHD to that expected in the general population.<sup>10</sup> All members of these families were invited for a clinical evaluation (between 1993-1995). Between 2002 and 2003, about one-third of the families (the largest families available who also had genome-wide anonymous markers typed by the Mammalian Genotyping Service) of the NHLBI FHS were invited to participate in a clinical examination that included measurement of CAC with cardiac CT. In addition to the initial NHLBI FHS study centers, an African-American center - University of Alabama at Birmingham - was recruited from the Hypertension Genetic Epidemiology Network Study, where subjects underwent cardiac CT but did not have dietary assessments. Of the 3360 subjects who had data on cardiac CT, 1084 subjects did not have data on egg consumption at baseline examination (1993-1995), 286 subjects were excluded for prevalent CHD, 68 subjects had missing data on covariates (56 for income; 5 for diabetes; 3 for hypertension; and 4 for physical activity), 18 subjects were non-white, and 56 subjects were excluded for extreme caloric intake (> 4200 and 3500 calories or <800 and 600 calories for men and women, respectively). The final sample size for current analyses was 1848. Each participant gave informed consent and the study protocol was reviewed and approved by each of the participating institutions.

## *2. Assessment of egg consumption*

Dietary information was collected through a staff-administered semi-quantitative food frequency questionnaire developed by Willett et al.<sup>11</sup> The reproducibility and validity of the food frequency questionnaire have been documented elsewhere.<sup>12-13</sup> Each subject was asked the following question: "In the past year, how often on average did you

consume eggs?" (Item #21 in the questionnaire forms). Possible responses were: almost never, 1-3/month, 1/week, 2-4/week, 5-6/week, 1/day, 2-3/day, 4-6/day, and >6/day. Due to sparse data, we collapsed adjacent categories while creating final exposure categories of almost never, 1-3/month, 1/week, and 2+/week for stable estimates.

### *3. Measurement of calcified atherosclerotic plaque in the coronary arteries*

Cardiac CT examinations were obtained using General Electric Health Systems LightSpeed Plus and LightSpeed Ultra, Siemens Volume Zoom, or Philips MX 8000 machines. Examinations were performed using the same protocol as employed in the NHLBI's Multi-Ethnic Study of Atherosclerosis.<sup>14</sup> The scans were performed using prospective ECG gating at 50% of the cardiac cycle, 120 KV, 106 mAs, 2.5 mm slice collimation, 0.5 s gantry rotation and a partial scan reconstruction resulting in a temporal resolution of between 250 and 300 ms. Images were reconstructed using the standard algorithm into a 35 cm display field-of-view. All subjects were imaged with a calcium calibration standard within the imaging field (Image Analysis, Columbia, KY). The scan through the heart was repeated after a 1-min pause during the same examination, resulting in two sequential scans for measurement of CAC. The effective radiation exposure for the average participant of each coronary scan was 1.5 mSv for men and 1.9 mSv for women. CT images from all sites were sent electronically to the central CT reading center located at Wake Forest University Health Sciences, Winston Salem, NC. Trained CT analysts using dedicated hardware (GE Advantage Windows Workstation) and software (GE Smar-Score) identified CAC in the epicardial coronary arteries and an Agatston score modified to account for slice thickness was calculated using a 130 CT number threshold and a minimum lesion size of 0.9 mm (i.e., 2 pixel connectivity filter).

Agatston score refers to the amount of calcium detected by the scan and is based on the area and the density of the calcified plaques.<sup>15</sup> In this report, the sum of the vessel plaque is reported as the total CAC score. Total CAC scores from the first and second measured were then averaged.

#### *4. Blood collection and assays*

All participants were asked to fast for 12 h before their arrival at the study center. Evacuated tubes without additives were used to collect samples for lipids. Triglyceride concentrations were measured using triglyceride GB reagent on the Roche COBAS FARA centrifugal analyzer (Boehringer Mannheim Diagnostics, Indianapolis). Serum total cholesterol was measured using a commercial cholesterol oxidase method on a Roche COBAS FARA centrifugal analyzer (Boehringer Mannheim Diagnostics, Indianapolis). HDL-cholesterol quantification was performed with the above described cholesterol method after precipitation of non-HDL-cholesterol with magnesium/dextran. For samples with triglyceride concentrations less than 4.5 mmol/L (400 mg/dL), LDL-cholesterol was calculated using the Friedewald formula.<sup>16</sup> For subjects with higher levels of triglycerides, LDL-cholesterol quantitation was performed on EDTA plasma by ultracentrifugation.

#### *5. Other variables*

Information on cigarette smoking, alcohol intake, and education was obtained by interview during the clinic visit. Resting blood pressure was measured three times on seated participants after a 5-minute rest using a random zero sphygmomanometer and an appropriate cuff size. For analyses, average systolic and diastolic blood pressures from



the second and third measurements were used. We used the seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure classification to define hypertension (stages 1 or 2; systolic blood pressure of at least 140 mm Hg or diastolic blood pressure of at least 90 mm Hg) or if the subject reported that, he/she was currently being treated for hypertension. Dietary information was obtained using a food frequency questionnaire. Level of physical activity during the previous year was estimated through self-reports. Anthropometric data were collected with participants wearing scrub suits. Diabetes mellitus was considered present if a subject was taking hypoglycemic agents, if a physician had told the subject that he/she had diabetes mellitus, or if fasting glucose was above 7 mmol/L. Prevalent CHD was defined as a self-reported history of myocardial infarction, percutaneous transluminal coronary angioplasty, or coronary artery bypass graft. All variables used in these analyses were ascertained during the initial examination (1993-1995) except for CAC scores, which were obtained during a follow-up examination (2002-2003).

#### 6. Statistical analysis

CAC was dichotomized into Agatston CAC score of 100+ versus less than 100, as described previously.<sup>17</sup> To correct for the effect of familial clustering, we used generalized estimating equations to calculate the prevalence odds ratios with corresponding 95% confidence interval for the presence of CAC across categories of egg consumption. Model 1 was adjusted for age (continuous) and sex. Model 2 adjusted for age, sex, field center, body mass index (continuous), smoking (current smoker Y/N), alcohol intake (current alcohol intake Y/N), physical activity (quartiles of total MET-min/wk), income (<\$25,000, \$25,000-<\$75,000, ≥\$75,000), bacon consumption (almost

never, 1-3/month, 1/week, and 2+/week), and caloric intake (continuous). Model 3 was additionally adjusted for history of hypertension (yes/no) and diabetes (yes/no).

In secondary analysis, we calculated the odds ratio per SD using different CAC cut-points (CAC >0 and CAC>50) as well as sex-specific analyses. All analyses were completed using SAS, version 9.2 (SAS institute Inc, Cary, NC). All p –values were 2-tailed and significance level was set at an alpha of 0.05.

## Results

Of the total 1848 subjects, 41% were men and the mean age was 56.5 years. **Table 1** shows the baseline characteristics by categories of egg consumption. Egg consumption was associated with younger age, higher body mass index, larger waist circumference, male sex, current smoking status; higher intake of dietary fiber, dietary cholesterol, saturated fat, magnesium, and total calories; and lower HDL. Subjects reporting egg consumption were less likely to exercise, and more likely to have diabetes mellitus. Of the 496 patients who consumed 2 eggs or more per week: 394 (79%) consumed 2-4/week; 10.1% consumed 5-6 eggs/wk; 7.9% consumed 1egg/day; 2.4% consumed 2-3 eggs/day; 0.2% consumed 4-6 eggs/day; and 0% consumed 6+ eggs/day.

There was no association between egg consumption and prevalent CAC. Compared to subjects reporting almost no egg consumption, multivariable adjusted odds ratio (95% CI) for CAC of 100+ were 1 (reference), 0.95 (0.66-1.38), 0.94 (0.63-1.40), and 0.90 (0.57-1.42) among subjects reporting egg consumption of <1/month, 1-3/month, 1/week, and 2+/week, respectively (p for linear trend 0.66, **Table 2**), adjusting for age, sex, BMI, smoking, alcohol, physical activity, income, field center, total calories, and

bacon. Further adjustment for hypertension and diabetes in the same model did not alter the conclusion: adjusted odds ratios were 1 (reference), 0.93 (0.64-1.34), 0.88 (0.58-1.32), and 0.90 (0.57-1.42) from the lowest to highest category of egg consumption, respectively (p for linear trend, 0.62, Table 2). Analysis restricted to individuals with diabetes mellitus or fasting glucose > 126 mg/dL did not show a significant association between egg consumption and prevalent CAC: adjusted odds ratios were 1 (reference), 1.28 (0.44-3.74), 1.29 (0.45-3.64), and 1.21 (0.36-4.09) among increasing categories of egg consumption, respectively (p for linear trend 0.76).

In a sensitivity analysis, there was no evidence of association between egg consumption and prevalent CAC when CAC cut points of 0 and 50 were used. Using CAC cut point of 0 to define prevalent CAC, the fully adjusted model showed adjusted odds ratios of 1 (reference), 0.97 (0.67-1.39), 0.99 (0.68-1.45), and 0.77 (0.52-1.14) from the lowest to highest category of egg consumption, respectively (p for linear trend, 0.22). Corresponding values with CAC cutpoint of 50 were 1 (reference), 1.23 (0.56-1.76), 1.05 (0.71-1.57), and 0.95 (0.62-1.45), respectively (p for linear trend, 0.62). Further adjustments for hypertension and diabetes and analyses restricted to diabetic individuals did not change the conclusions.

## Discussion

In this study, we did not find an association between egg consumption and prevalent CAC in adult subjects free of prevalent CHD. The fully adjusted model and an additional model controlling for both hypertension and diabetes did not show an association. The lack of association was also observed when using CAC cut points of 0 and 50 and when

analyses were restricted to individuals with diabetes mellitus.

There has been a significant research interest in egg consumption as a possible mediator for cardiovascular disease owing to the large amount of dietary cholesterol in eggs. Other studies have investigated the effects of egg consumption on coronary heart disease<sup>18-20</sup>, stroke<sup>21</sup>, and carotid artery plaque burden.<sup>22</sup> More recently, Chagas et al. found an inverse association between egg consumption and coronary atherosclerotic burden as determined by angiography.<sup>23</sup> To our knowledge, this is the first study to examine whether egg consumption is associated with prevalent CAC.

While one prospective cohort of 514 Australian Aborigines with ~14 years of follow-up showed an increased risk of CHD in subjects consuming >2 eggs per week<sup>18</sup>, the majority of prospective cohort studies have found no association between egg consumption and risk of CHD.<sup>19-20</sup> The latter finding was further supported by a recent meta-analysis of six studies between 1999-2011.<sup>4</sup> However, another recent systematic meta-analysis found a dose-response relationship between egg consumption and both cardiovascular disease (CVD) and diabetes.<sup>5</sup> In the analysis by Li et al<sup>5</sup>, twelve relevant papers were selected using coronary heart disease, ischemic heart disease, and congestive heart failure as CVD outcomes. Their findings of increased risk of CVD with increasing egg consumption contrasts with the majority of findings in recent literature, while the positive association between egg consumption and risk of CVD in both diabetic men and women in the US has been supported by few studies.<sup>19-20</sup> Indeed, in a prospective cohort study of Greek adult diabetics, consumption of one egg (~40gm) was associated with a fivefold increased risk of death by CHD.<sup>24</sup>

The relationship between egg nutrient components, namely cholesterol, and their cardiometabolic effects remains unclear. Physiologic evidence has supported individual variation (hyperresponders vs. hyporesponders) in fasting lipid responses to dietary cholesterol.<sup>25</sup> Epidemiological data from a meta-analysis that included over 500 patients across three continents, however, showed that dietary cholesterol significantly increased the total to HDL- cholesterol ratio, suggesting the increase in protective HDL is offset by a greater rise in LDL and other non-HDL cholesterol.<sup>26</sup> More recent evidence suggests that postprandial oxidative stress and inflammation from dietary cholesterol may confer risk independent of lipid profiles.<sup>27</sup> Furthermore, the phosphatidylcholine (lecithin) content of eggs may confer CVD risk independently of changes in lipid profile; recent research has demonstrated that its pro-atherosclerotic metabolite, trimethylamine-N-oxide (TMAO), is associated with increased incident risk of major CVD events.<sup>28</sup>

Individuals with diabetes have demonstrated abnormal cholesterol profiles and may have impaired cholesterol transport.<sup>29-30</sup> The influence of egg on the cholesterol profile in an abnormal host could help explain the increased risk of CHD in diabetic populations. Our analysis, however, did not reveal a significant association between increasing egg consumption and prevalent CAC in individuals with diabetes mellitus, suggesting that the development of atherosclerotic coronary artery disease may not be significantly influenced by egg consumption. Alternatively, egg consumption might be associated with other healthful factors that could offset any detrimental effects of dietary cholesterol or glycerolipid species contained in eggs.

Limitations of the current study include its observational design, self-reported egg consumption that could have been inaccurate, and a lack of details on how eggs were

consumed (e.g. egg with or without yolk, fried egg, boiled egg). Furthermore, eggs are often consumed in conjunction with other food items, including processed red meats and breadstuffs; thus egg consumption may be a marker of specific dietary patterns. We only had baseline dietary assessment and were unable to capture changes in dietary habits that may have occurred over time and could affect CAC outcomes. It is also possible that a lack of an association between egg consumption and CAC may be partially due to a younger age of our population and the fact that coronary calcium assessment may only identify calcified plaques. The subgroup analysis of diabetic individuals had a small sample size and thus our ability to draw conclusions is limited. Furthermore, we had one single measurement of CAC and cannot account for change in CAC over time nor distinguish CAC development unrelated to egg intake.

Strengths of this study include the detailed dietary questionnaire; a large sample size; and robustness of findings in sensitivity analyses using various cut points to define prevalent CAC.

In conclusion, we found no relationship between egg consumption and prevalent CAC in this population.

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JMR and LD designed research; all authors conducted research; ABP and LD analyzed data and performed statistical analyses; JMR and LD wrote the paper. All authors provided critical revisions for content and had responsibility for the final content. Appreciation is expressed to the staff of the study and especially to the study participants who volunteered for the project.



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297 **Conflict of interest:**

298 None of the authors has a conflict of interest to disclose.



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397

398 **Table 1**

399 Characteristics among 1848 participants of the NHLBI Family Heart Study according  
 400 to egg consumption

		Frequency of Egg Consumption				
		Almost Never (n = 361)	1-3/month (n = 476)	1/week (n = 515)	2+/week (n = 496)	p for linear trend
Age (y)		58.4 ± 12.8	55.6 ± 12.8	56.6 ± 13.0	55.7 ± 12.8	0.0110
BMI (kg/m <sup>2</sup> )		28.0 ± 5.4	28.5 ± 5.4	28.8 ± 5.7	29.6 ± 5.9	<0.0001
Male (%)		38.0	38.5	39.6	48.2	0.0017
Current Smoker (%)		8.0	6.9	9.3	12.3	0.0096
Current Drinker (%)		50.1	54.6	51.3	49.2	0.4502
History of hypertension (%)		32.4	35.9	40.8	34.9	0.3046
History of diabetes (%)		7.8	7.8	10.9	11.1	0.0345
Income (%)						
	<\$25,000	12.7	12.8	11.8	11.5	0.4874
	\$25,000 - <\$75,000	51.8	49.6	55.2	59.9	0.0031
	≥\$75,000	35.5	37.6	33.0	28.6	0.0083
Almost never eats bacon (%)		80.3	55.3	38.8	25.0	<0.0001
LDL (mg/dl)		114.3 ± 32.2	112.3 ± 31.5	114.2 ± 33.8	112.7 ± 34.7	0.6964
HDL (mg/dl)		50.2 ± 13.4	50.1 ± 14.9	49.9 ± 15.0	47.9 ± 14.3	0.0220
Waist Circumference (cm)		95.8 ± 15.4	97.4 ± 16.0	98.3 ± 16.0	100.9 ± 16.1	<0.0001
Exercise (MET-min/week)		825.7 ± 1294.7	760.0 ± 874.1	661.0 ± 895.9	684.8 ± 1060.2	0.0191
Fruit and Veg (s/day)		4.7 ± 2.4	4.2 ± 2.4	4.0 ± 2.3	4.0 ± 2.5	0.0873
Dietary Fiber (g/d)		16.4 ± 7.8	16.0 ± 7.2	16.1 ± 7.3	18.0 ± 8.3	0.0021
Calories (kcal/d)		1545.1 ± 555.7	1639.9 ± 7.2	1726.3 ± 569.4	2008.5 ± 636.8	<0.0001
Saturated fat (g/d)		17.9 ± 9.8	20.5 ± 9.8	22.2 ± 9.5	27.7 ± 11.1	<0.0001
Dietary Magnesium (mg/d)		241.2 ± 87.8	250.0 ± 91.4	255.7 ± 89.4	283.2 ± 102.2	<0.0001
Dietary Cholesterol (g/d)		162.8 ± 83.8	196.0 ± 86.1	223.3 ± 89.4	344.5 ± 131.7	<0.0001

401

402

403 **Table 2**

404 Prevalence odds ratios (95% confidence intervals) of calcified atherosclerotic plaque  
 405 in the coronary arteries according to egg consumption in 1848 participants in the  
 406 NHLBI Family Heart Study.

407

Frequency of Egg Consumption	Cases/n	Crude	Age and Sex adjusted	Model 2 <sup>a</sup>	Model 3 <sup>b</sup>
<b>Almost never</b>	97/361	1.00	1.00	1.00	1.00
<b>1-3/month</b>	104/476	0.76 (0.57-1.02)	0.96 (0.58-1.37)	0.95 (0.66-1.38)	0.93 (0.64-1.34)
<b>1/week</b>	124/515	0.86 (0.64-1.17)	0.98 (0.67-1.42)	0.94 (0.63-1.40)	0.88 (0.58-1.32)
<b>2+/week</b>	110/496	0.78 (0.57-1.06)	0.79 (0.54-1.16)	0.90 (0.57-1.42)	0.90 (0.57-1.42)
<b>p for trend</b>		0.2410	0.2639	0.6600	0.6213

408

409 <sup>a</sup> Adjusted for age, sex, BMI, smoking, alcohol, physical activity, income, field center,

410 total calories, bacon

411 <sup>b</sup> Adjusted as in model 2 plus additional adjustment for hypertension and diabetes

412 mellitus

413